Rafael Moure
University of Lowell
Lowell, Massachusetts

Thomas E. Norris
School of Medicine
University of North Dakota
Grand Forks, North Dakota

Cecil B. Pikett
Schering Plough Research Institute
Kenilworth, New Jersey

Macolm C. Pike
University of Southern California
Los Angeles, California

George Provenzano
University of Maryland
Baltimore, Maryland

Donald J. Reed
Orgeon State University
Corvallis, Oregon

Mary Vore
College of Medicine
University of Kentucky
Lexington, Kentucky

I. Bernard Weinstein
Columbia-Presbyterian Cancer Center
New York, New York

Inflammation: More Than One Explanation

I read with interest the *EHP* supplement on oxygen radicals and lung injury (vol. 102, supplement 10). I would like to take this opportunity to comment about this supplement and raise a key issue concerning the major concepts regarding the mechanisms of cellular injury in inflammatory diseases.

As an active investigator in this field of research, I cannot fully understand why there was no mention in the supplement about the basic understanding that cellular damage in inflammation is multifactorial. The nonexpert reader of this supplement might receive an erroneous impression that oxygen radicals, per se, are the exclusive toxic agonists that induce cellular injury. Many in this field share the view that cellular damage in inflammatory diseases might be caused by a "coordinated cross-talk" among oxidants, membrane-damaging agents, proteinases, arachidonic acid metabolites, phospholipases, cationic proteins, and cytokines. All these agents are likely to be present in sites of infection and inflammation. But sadly, none of the publications elaborating on this multifactorial view are quoted in modern textbooks or in symposia on inflammation and inflammatory diseases. Instead, the literature is filled with publications that insist on a single agonist, be it an oxidant, a protease, a cytokine, etc., in experimental models. No attempt to integrate the various agonists into the full picture is made.

Several of our publications (*1–7*) deal with synergistic interactions among multiple proinflammatory agonists in cellular injury during inflammation. I believe that this issue is important, timely, and might contribute to an understanding of how drugs, chemicals, and xenobiotics function *in vivo*.

Isaac Ginsburg
Hadassah School of Dental Medicine
Hebrew University
Jerusalem

References

1. Ginsburg I, Kohen R. Synergistic effects among oxidants, membrane-damaging agents, fatty acids, proteinases, and xenobiotics: killing of epithelial cells and release of arachidonic acid. Inflammation 19:101–118 (1995)
2. Ginsburg I, Kohen R, Ligumsky M. Ethanol synergizes with hydrogen peroxide, peroxyl radical, and trypsin to kill epithelial cells in culture. Free Rad Biol Med 16:263–269 (1994).
3. Ginsburg I. Can hemolytic streptococci be considered "forefathers" of modern phagocytes? Comp Biochem Physiol C 109:147–158 (1994).
4. Ginsburg I, Mitra RS, Gibbs DF, Varani J, Kohen R. Killing of endothelial cells and release of arachidonic acid: synergistic effects among hydrogen peroxide, membrane-damaging agents, cationic substances, and proteinases and their modulation by inhibitors. Inflammation 17:295–319 (1993).
5. Ginsburg I, Misgav R, Pinson A, Varani J, Ward PA, Kohen R. Synergism among oxidants, proteinases, phospholipases, microbial hemolysins, cationic proteins, and cytokines. Inflammation 16:519–538 (1992).
6. Ginsburg I, Gibbs DF, Schuger L, Johnson KJ, Ryan US, Ward PA, Varani J. Vascular endothelial cell killing by combinations of membrane-active agents and hydrogen peroxide. Free Rad Biol Med 7:369–376 (1989).
7. Varani J, Ginsburg I, Schuger L, Gibbs DF, Bromberg J, Johnson KJ, Ryan US, Ward PA. Endothelial cell killing by neutrophils: synergistic interaction of oxygen products and proteases. Am J Pathol 135:435–438 (1989).

Response

We appreciate the interest shown by Dr. Ginsburg in our recent conference proceedings (*EHP* 102, supplement 10). As stated in the preface of those proceedings, The Oxygen Radicals and Lung Injury Conference was the first of its kind dedicated to pulmonary science. Therefore, in this conference, the primary attempt was to focus on oxygen radicals and their involvement in toxic insults and the ensuing pathophysiological processes in the lung. We did not ignore the importance of multifactorial relationships of other cellular reactions and products involved in cellular damage and injury. In fact, these issues were addressed in the presentations of Ward (*1*), Holian et al. (*2*), Repine (*3*), Torphy et al. (*4*), and Demers and Kuhn (*5*). The complex network of micromolecular reactions have not been fully defined to understand the coordination, modulation, and integration of cellular functions. In many pulmonary diseases (e.g., cancer, emphysema, pneumoconiosis) in which oxygen radicals are implicated, the disease becomes evident only after several years. Subtle damage or changes to biomolecules and their relationships to the coordination and interactions of oxygen radical generation and degradation are important issues to be dealt with in greater detail to understand the synergistic concepts of lung dieases. We hope that future conferences will address these and other issues.

V. Vallythan
V. Castranova
K. Weber
National Institute of Occupational
Safety and Health
Morgantown, West Virginia

References

1. Ward PA. Oxygen radicals, cytokines, adhesion molecules, and lung injury. Environ Health Perspect 102(Suppl 10):13–16 (1994).
2. Holian A, Kelley K, Hamilton RF Jr. Mechanisms associated with human alveolar macrophage stimulation by particulates. Environ Health Perspect 102(Suppl 10):69–74 (1994).
3. Repine JE. Interleukin-1-mediated acute lung injury and tolerance to oxidative injury. Environ Health Perspect 102(Suppl 10): 75–78 (1994).
4. Torphy TJ, Barnette MS, Hay DWP, Underwood DC. Phophodiesterase IV inhibitors as therapy for eosinophil-induced lung injury in asthma. Environ Health Perspect 102(Suppl 10):79–84 (1994).
5. Demers LM, Kuhn DC. Influence of mineral dusts on metabolism of arachidonic acid by alveolar macrophage. Environ Health Perspect 102(Suppl 10):97–100 (1994).

MTBE: Not Carcinogenic

Subsequent to publication of *EHP*'s timely article on the toxicological potential of methyl-*tert*-butyl ether (MTBE; vol. 103, pp. 666–670), the long-awaited study from the Ramazzini Foundation of Oncology and Environmental Sciences appeared in print (*1*). This was a landmark publication because for months we in the scientific community had been advised that the data predicted dire health hazards for humans exposed